REMARKS

Claims 1-8 are pending in the instant application. Claims 1-8 have been rejected. Claim 5 has been amended. Claims 2 and 6 have been canceled. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Objection to the Claims

Claims 5-6 have been objected to for reciting "paclitaxol". The Examiner suggests replacing "paclitaxol" with "paclitaxel". Applicant has made the appropriate correction and respectfully requests that this objection be withdrawn.

II. Rejection Under 35 U.S.C. §102

Claims 1-2 have been rejected under 35 U.S.C. 102(a) or (b) as being anticipated by Zheng et al. ((2000) *Oncol. Res.* 12:419-27). It is suggested that Zheng et al. disclose the synergistic effects of a combination composition comprising all-trans retinoic acid and 12-O-tetradecanoylphorbol-13-acetate (TPA) against HL-60 leukemia cells. It is suggested that because the prior art combination composition would be capable of performing the claimed intended use, the prior art anticipates the claims. Applicant respectfully traverses this rejection.

Zheng et al. is Applicant's own publication published within the one year grace period allowed under 35 U.S.C. §102(b). As such, Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Accordingly, Applicant submits herewith a

1.132 Declaration by Allan H. Conney indicating that Zheng et al. is not by another nor was it published more than twelve months prior to the present application. Therefore, Zheng et al. is not a prior art reference under 102(a) and 102(b). In light of the enclosed Declaration and the accompanying remarks, reconsideration and withdrawal of this rejection is respectfully requested.

III. Rejection Under 35 U.S.C. §103

Claims 3-4 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Grant et al. (WO 02/22133) and Powell et al. ((1996) *Cell Growth Differ.* 7:419-28) in view of Farmer et al. (U.S. Patent No. 6,005,007) and Sporn et al. (U.S. Patent No. 5,821,254). The Examiner suggests that Grant et al. disclose a method of promoting apoptosis in cancer cells such as prostate cancer cells, the method comprising administering an effective amount of an agent that induces cellular differentiation and a cyclin dependent kinase inhibitor. It is suggested that this references teaches PMA (*i.e.,* TPA) and retinoids such as all-trans retinoic acid as specific agents for inducing cellular differentiation.

The Examiner suggests that Powell et al. disclose that PMA induces apoptosis in androgen-sensitive prostate cancer cells.

Further, it is suggested that while Grant et al. and Powell et al. do not specifically disclose treating prostate cancer in a patient comprising administering a composition comprising PMA and a retinoid, Farmer et al. disclose a method for treating cancer, such as prostate cancer, by administering an effective amount of a retinoid compound and Sporn et al. teach the use of 9-cis-

retinoic acid compounds in the treatment of cancers such as prostate cancer.

The Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Grant et al. and Powell et al. to treat prostate cancer by administering a composition containing PMA and the retinoids of Farmer et al. and Sporn et al. because one of ordinary skill in the art would reasonably expect the additive effect of the two compounds to be effective in inhibiting the growth of prostate cancer cells thereby treating the patient suffering from prostate cancer. Applicant respectfully traverses this rejection.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure.* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

Applicant respectfully believes that the Examiner has used impermissible hindsight in combining the cited references as there is simply no teaching, suggestion or motivation to make such a combination in the references themselves or in the knowledge generally available to one of ordinary skill in the

art, particularly with the referenced teachings in hand. Specifically, Grant et al. teach a method for promoting apoptosis in cancer cells by co-administering a cyclin-dependent kinase inhibitor with an agent that induces cell differentiation (*e.g.*, PMA or all-trans retinoic acid). This reference does not teach or suggest the use of an agent that induces cell differentiation in the absence of a cyclin-dependent kinase inhibitor nor does Grant et al. teach or suggest the use of PMA in combination with a retinoid. Likewise, Powell et al., Farmer et al., and Sporn et al. are silent to the use of PMA in combination with a retinoid. Therefore, the cited references do not satisfy the requirement set forth at MPEP 2142 because they fail to provide within the references themselves the teaching or suggestion to make the claimed combination.

Further, as required by MPEP 2143.01, the prior art must suggest the desirability of the combination. In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). In this regard, Grant et al. teaches that PMA and a retinoid are alternate choices for "an agent that induces cell differentiation" for carrying out the method of the invention. As such, there would be little desirability for the skilled artisan to use PMA and a retinoid in combination because Grant et al. teaches they are interchangeable.

Moreover, Grant et al. teach that a suitable dose of an agent that induces cell differentiation is in the range of about 50 nM to 10 μM (see page 10, lines 8-11). Likewise, Powell et al. teach 10 nM doses of PMA to achieve the effect of decreasing prostate cancer cell growth. In contrast, the instant specification teaches that lower therapeutically effective doses

of PMA can be employed (*e.g.*, the clinically relevant doses of 0.16 to 0.32 nM disclosed at page 12, lines 1-8) when PMA is used in combination with a retinoid. Therefore, as defined by the teachings of the instant invention, a therapeutically effective dose of PMA is lower and non-obvious based upon the synergistic effect afforded by the claimed combination.

Accordingly, because the suggestion, motivation, and desirability to modify or combine the referenced teachings is lacking, the claimed invention is not obvious in accord with the requirements set forth in MPEP 2142 and 2143.01. It is therefore respectfully requested that this rejection be withdrawn.

Claims 5-8 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Grant et al. and Powell et al. in view of Broder et al. (U.S. Patent No. 6,395,770). It is suggested that while Grant et al. and Powell et al. do not disclose a method for treating prostate cancer by administering a composition comprising PMA in combination with paclitaxel, Broder et al. disclose a method of treating cancers such as prostate cancer by orally administering to a patient an effective amount of paclitaxel. The Examiner suggests it would have been obvious to one of ordinary skill in the art to combine PMA and paclitaxel because there would have been a reasonable expectation that the apoptosis-inducing activity of PMA and the cytotoxic activity of paclitaxel combined would effectively inhibit and thereby treat prostate cancer. Applicant respectfully traverses this rejection.

Grant et al. and Powell et al. do not teach PMA in combination paclitaxel. Broder et al. teach a composition comprising a derivative or analog of paclitaxel or docetaxel and an oral bioavailability enhancing agent comprising a cyclosporin

and methods for using the same. This reference does not teach or suggest paclitaxel in combination with PMA. Accordingly, the cited references do not satisfy the requirement set forth at MPEP 2142 because they fail to provide within the references themselves the teaching or suggestion to make the claimed combination.

Further, this reference fails to suggest the desirability of the combination (MPEP 2143.01) because "the taxane class of antineoplastic agents, particularly paclitaxel, can be orally administered to human beings with substantial and therapeutic blood levels being achieved, and with no undue toxicity or adverse side effects observed even without pre-administration of medications to prevent adverse reactions." As such, one of skill in the art would have little motivation to modify the teachings of Broder et al. because the method therein achieves substantial and therapeutic blood levels of paclitaxel thereby increasing its the activity.

As discussed *supra*, Grant et al. teach that a suitable dose of PMA is in the range of about 50 nM to 10 μM and Powell et al. teach 10 nM PMA. Broder et al. teach that "[t]he method of the invention makes it possible to administer paclitaxel and other taxanes orally ranging from about 20 mg/m^2 to about 1000 mg/m^2 (based on patient body surface area) or about 2-30 mg/kg (based on patient body weight) as single or divided (2-3) daily doses, and maintain the plasma levels of paclitaxel in humans in the range of 50-500 ng/ml for extended periods of time (e.g., 8-12 hours) after each oral dose." In contrast, the instant application teaches that paclitaxel, when used in combination with low therapeutically effective doses of PMA (*e.g.*, 1 ng/ml or

1.6 nM; Table 4 of the specification), can achieve a therapeutic effect at doses of 5 ng/ml which are significantly lower than those disclosed by Broder et al. Therefore, as defined by the teachings of the instant invention, a therapeutically effective dose of PMA and paclitaxel is lower and non-obvious based upon the synergistic effect afforded by the claimed combination.

Accordingly, because the suggestion, motivation, and desirability to modify or combine the referenced teachings is lacking, the claimed invention is not obvious in accord with the requirements set forth in MPEP 2142 and 2143.01. It is therefore respectfully requested that this rejection be withdrawn.

The Examiner has indicated that should claims 1 and 2 as well as claims 5 and 6 be found allowable, claims 1-2 and 5-6 will be objected to under 37 CFR 1.75 as being substantially duplicate thereof. Accordingly, to facilitate the prosecution of the instant application, Applicant is canceling claims 2 and 6.

IV. Conclusion

The Applicant believes that the foregoing comprises a full and complete response to the Office Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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